

LISTING OF CLAIMS

1. (Previously Presented) A nimesulide composition comprising:
 - (a) particles of nimesulide or a salt thereof, wherein the particles have an effective average particle size of less than 2000 nm; and
 - (b) at least one surface stabilizer adsorbed on the surface of the nimesulide particles.
2. (Previously Presented) The composition of claim 1, wherein the nimesulide is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.
3. (Previously Presented) The composition of claim 1, wherein the effective average particle size of the nimesulide particles is selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 100 nm, less than 75 nm, and less than 50 nm.
4. (Original) The composition of claim 1, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.
5. (Original) The composition of claim 1 formulated into a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.
6. (Original) The composition of claim 1, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

7. (Original) The composition of claim 1, wherein the nimesulide or a salt thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined dry weight of the nimesulide or a salt thereof and at least one surface stabilizer, not including other excipients.

8. (Original) The composition of claim 1, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the nimesulide or a salt thereof and at least one surface stabilizer, not including other excipients.

9. (Original) The composition of claim 1, comprising two or more surface stabilizers.

10. (Previously Presented) The composition of claim 1, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, a non-ionic surface stabilizer, and an ionic surface stabilizer.

11. (Original) The composition of claim 10, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-

N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, and random copolymers of vinyl acetate and vinyl pyrrolidone.

12. (Original) The composition of claim 10, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

13. (Previously Presented) The composition of claim 10, wherein the surface stabilizer is selected from the group consisting of cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-

didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearylalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

14. (Original) The composition of claim 1, comprising as a surface stabilizer a random copolymer of vinyl acetate and vinyl pyrrolidone, hydroxypropylmethyl cellulose, or tyloxapol.

15. (Original) The composition of any of claims 10, 12, or 13, wherein the composition is bioadhesive.

16. (Original) The composition of claim 1, wherein the T_{max} of the nimesulide, when assayed in the plasma of a mammalian subject following administration, is less than the T_{max} for a conventional, non-nanoparticulate form of nimesulide, administered at the same dosage.

17. (Previously Presented) The composition of claim 16, wherein the T_{max} is selected from the group consisting of not greater than 90%, not greater than 80%, not greater than 70%, not greater than 60%, not greater than 50%, not greater than 30%, not greater than 25%, not greater than 20%, not greater than 15%, and not greater than 10% of the T_{max}, exhibited by a non-nanoparticulate formulation of nimesulide, administered at the same dosage.

18. (Original) The composition of claim 1, wherein the C_{\max} of the nimesulide, when assayed in the plasma of a mammalian subject following administration, is greater than the C_{\max} for a conventional, non-nanoparticulate form of nimesulide, administered at the same dosage.

19. (Previously Presented) The composition of claim 18, wherein the C_{\max} is selected from the group consisting of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, and at least 100% greater than the C_{\max} exhibited by a non-nanoparticulate formulation of nimesulide, administered at the same dosage.

20. (Original) The composition of claim 1, wherein the AUC of the nimesulide, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a conventional, non-nanoparticulate form of nimesulide, administered at the same dosage.

21. (Previously Presented) The composition of claim 20, wherein the AUC is selected from the group consisting of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, and at least 100% greater than the AUC exhibited by a non-nanoparticulate formulation of nimesulide, administered at the same dosage.

22. (Previously Presented) The composition of claim 1 which does not produce a difference in the absorption levels of the nimesulide composition when administered to a patient under fed as compared to fasting conditions.

23. (Previously Presented) The composition of claim 22, wherein the difference in absorption of the nimesulide composition of the invention, when administered in the fed versus the fasted state, is selected from the group consisting of less than 100%, less than 90%, less than 80%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, and less than 3%.

24. (Original) The composition of claim 1, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, when administered to a human.

25. (Original) The composition of claim 24, wherein “bioequivalency” is established by a 90% Confidence Interval of between 0.80 and 1.25 for both C_{\max} and AUC, when administered to a human.

26. (Original) The composition of claim 24, wherein “bioequivalency” is established by a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for C_{\max} , when administered to a human.

27. (Previously Presented) The composition of claim 1, further comprising at least one additional nimesulide composition having an effective average particle size which is different than the effective average particle size of the nimesulide composition of claim 1.

28. (Previously Presented) The composition of claim 1, wherein upon administration the composition redisperses such that the nimesulide particles have an effective average particle size of less than 2000 nm.

29. (Previously Presented) The composition of claim 28, wherein upon administration the composition redisperses such that the nimesulide particles have an effective average particle size selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 150 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

30. (Previously Presented) The composition of claim 1, wherein the composition redisperses in a biorelevant media such that the nimesulide particles have an effective average particle size of less than 2 microns.

31. (Previously Presented) The composition of claim 30, wherein the composition redisperses in a biorelevant media such that the nimesulide particles have an effective average particle size selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than

1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 150 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

32. (Withdrawn) The composition of claim 1 formulated into a liquid dosage form, wherein the dosage form has a viscosity of less than 2000 mPa·s, measured at 20°C, at a shear rate of 0.1 (1/s).

33. (Withdrawn) The composition of claim 32, having a viscosity at a shear rate of 0.1 (1/s) selected from the group consisting of from about 2000 mPa·s to about 1 mPa·s, from about 1900 mPa·s to about 1 mPa·s, from about 1800 mPa·s to about 1 mPa·s, from about 1700 mPa·s to about 1 mPa·s, from about 1600 mPa·s to about 1 mPa·s, from about 1500 mPa·s to about 1 mPa·s, from about 1400 mPa·s to about 1 mPa·s, from about 1300 mPa·s to about 1 mPa·s, from about 1200 mPa·s to about 1 mPa·s, from about 1100 mPa·s to about 1 mPa·s, from about 1000 mPa·s to about 1 mPa·s, from about 900 mPa·s to about 1 mPa·s, from about 800 mPa·s to about 1 mPa·s, from about 700 mPa·s to about 1 mPa·s, from about 600 mPa·s to about 1 mPa·s, from about 500 mPa·s to about 1 mPa·s, from about 400 mPa·s to about 1 mPa·s, from about 300 mPa·s to about 1 mPa·s, from about 200 mPa·s to about 1 mPa·s, from about 175 mPa·s to about 1 mPa·s, from about 150 mPa·s to about 1 mPa·s, from about 125 mPa·s to about 1 mPa·s, from about 100 mPa·s to about 1 mPa·s, from about 75 mPa·s to about 1 mPa·s, from about 50 mPa·s to about 1 mPa·s, from about 25 mPa·s to about 1 mPa·s, from about 15 mPa·s to about 1 mPa·s, from about 10 mPa·s to about 1 mPa·s, and from about 5 mPa·s to about 1 mPa·s.

34. (Withdrawn) The composition of claim 32, wherein the viscosity of the dosage form is selected from the group consisting of less than 1/200, less than 1/100, less than 1/50, less than 1/25, and less than 1/10 of the viscosity of a liquid dosage form of conventional non-nanoparticulate nimesulide at about the same concentration per ml of nimesulide.

35. (Withdrawn) The composition of claims 32, wherein the viscosity of the dosage form is selected from the group consisting of less than 5%, less than 10%, less than 15%, less than 20%, less than 25%, less than 30%, less than 35%, less than 40%, less than 45%, less than 50%, less than 55%, less than 60%, less than 65%, less than 70%, less than 75%, less than 80%,

less than 85%, and less than 90% of the viscosity of a liquid dosage form of conventional, non-nanoparticulate nimesulide at about the same concentration per ml of nimesulide.

36. (Original) The composition of claim 1, additionally comprising one or more non-nimesulide active agents.

37. (Previously Presented) The composition of claim 36, wherein said non-nimesulide active agent is selected from the group consisting of an analgesic, an anti-inflammatory, an antipyretic, and a vasomodulator.

38. (Original) The composition of claim 36, wherein said non-nimesulide active agent is selected from the group consisting of nutraceuticals, proteins, peptides, nucleotides, amino acids, anti-obesity drugs, central nervous system stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, NSAIDs, non-nimesulide COX-2 inhibitors, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, vasomodulators, and xanthines.

39. (Withdrawn) The composition of claim 38, wherein said nutraceutical is selected from the group consisting of lutein, folic acid, fatty acids, fruit extracts, vegetable extracts, vitamin supplements, mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids, green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish oils, marine animal oils, and probiotics.

40. (Original) The composition of claim 36, wherein said non-nimesulide active agent is selected from the group consisting of aceclofenac, acemetacin, e-acetamidocaproic acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic acid, S-adenosylmethionine, alclofenac, alfentanil, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amfenac, aminochlorthenoxazin, 3-amino-4-hydroxybutyric acid, 2-amino-4-picoline, aminopropylon, aminopyrine, amixetrine, ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitramide, α -bisabolol, bromfenac, p-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, bucetin, bucloxic acid, bucolome, buprenorphine, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphen, carprofen, carsalam, chlorobutanol, chlorthenoxazin, choline salicylate, cinchophen, cinmetacin, ciramadol, clidanac, clometacin, clonitazene, clonixin, clopirac, clove, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, cropropamide, crotethamide, desomorphine, dexoxadrol, dextromoramide, dezocine, diampromide, diclofenac sodium, difenamizole, difenpiramide, diflunisal, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrone, ditazol, droxicam, emorfazone, enfenamic acid, epirizole, eptazocine, etersalate, ethenzamide, ethoheptazine, ethoxazene, ethylmethylthiambutene, ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradinol, feprazone, floctafenine, flufenamic acid, flunoxaprofen, fluoresone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentisic acid, glafenine, glucametacin, glycol salicylate, guaiazulene, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, ibuprofen, ibuproxam, imidazole salicylate, indomethacin, indoprofen, isofezolac, isoladol, isomethadone, isonixin, isoxepac, isoxicam, ketobemidone, ketoprofen, ketorolac, p-lactophenetide, lefetamine, levorphanol, lofentanil, lonazolac, lomoxicam, loxoprofen, lysine acetylsalicylate, magnesium acetylsalicylate, meclofenamic acid, mefenamic acid, meperidine, meptazinol, mesalamine, metazocine, methadone hydrochloride, methotrimeprazine, metiazinic acid, metofoline, metopon, mofebutazone, mofezolac, morazone, morphine, morphine hydrochloride, morphine sulfate, morpholine salicylate, myrophine, nabumetone, nalbuphine, 1-naphthyl salicylate, naproxen,

narceine, nefopam, nicomorphine, nifenazone, niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide, norlevorphanol, normethadone, normorphine, norpipanone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin, oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paranyline, parsalmide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenylramidol, piketoprofen, piminodine, pipebuzone, piperylone, pirofen, pirazolac, piritramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene, propyphenazone, proquazone, protizinic acid, ramifenazone, remifentanyl, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide o-acetic acid, salicylsulfuric acid, salsalte, salverine, simetride, sodium salicylate, sufentanyl, sulfasalazine, sulindac, superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofenic acid, tiaramide, tilidine, tinoridine, tolfenamic acid, tolmetin, tramadol, tropesin, viminol, xenbucin, ximoprofen, zaltoprofen, and zomepirac.

41. (Withdrawn) The composition of claim 38, in which the vasomodulator is selected from the group consisting of caffeine, theobromine, and theophylline.

42. (Withdrawn) The composition of claim 38, in which the NSAID is selected from the group consisting of nabumetone, tiaramide, proquazone, bufexamac, flumizole, epirazole, tinoridine, timegadine, dapsone, aspirin, diflunisal, benorylate, fosfosal, diclofenac, alclofenac, fenclofenac, etodolac, indomethacin, sulindac, tolmetin, fentiazac, tilomisolet, carprofen, fenbufen, flurbiprofen, ketoprofen, oxaprozin, suprofen, tiaprofenic acid, ibuprofen, naproxen, fenoprofen, indoprofen, pirofen, flufenamic, mefenamic, meclofenamic, niflumic, oxyphenbutazone, phenylbutazone, apazone, feprazone, piroxicam, sudoxicam, isoxicam, and tenoxicam.

43. (Withdrawn) The composition of claim 38, in which the COX-2 inhibitor is selected from the group consisting of celecoxib, rofecoxib, meloxicam, valdecoxib, parecoxib, etoricoxib, SC-236, NS-398, SC-58125, SC-57666, SC-558, SC-560, etodolac, DFU, monteleukast, L-745337, L-761066, L-761000, L-748780, DUP-697, PGV 20229, iguratimod, BF 389, CL 1004, PD 136005, PD 142893, PD 138387, PD 145065, flurbiprofen, nabumetone,

flosulide, piroxicam, diclofenac, lumiracoxib, D 1367, R 807, JTE-522, FK-3311, FK 867, FR 140423, FR 115068, GR 253035, RWJ 63556, RWJ 20485, ZK 38997, S 2474, zomepirac analogs, RS 104894, SC 41930, pranlukast, SB 209670, and APHS

44. (Original) The composition of claim 1, which has been sterile filtered.

45. (Withdrawn) A method of making a nimesulide composition comprising contacting particles of nimesulide or a salt thereof with at least one surface stabilizer for a time and under conditions sufficient to provide a nimesulide composition having an effective average particle size of less than 2000 nm, wherein the at least one surface stabilizer is adsorbed on the surface of the nimesulide particles.

46. (Withdrawn) The method of claim 45, wherein said contacting comprises grinding.

47. (Withdrawn) The method of claim 46, wherein said grinding comprises wet grinding.

48. (Withdrawn) The method of claim 45, wherein said contacting comprises homogenizing.

49. (Withdrawn) The method of claim 45, wherein said contacting comprises:

(a) dissolving the particles of nimesulide or a salt thereof in a solvent;
(b) adding the resulting nimesulide solution to a solution comprising at least one surface stabilizer; and

(c) precipitating the solubilized nimesulide having at least one surface stabilizer adsorbed on the surface thereof by the addition thereto of a non-solvent.

50. (Withdrawn) The method of claim 45, wherein the nimesulide or a salt thereof is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.

51. (Withdrawn) The method of claim 45, wherein the effective average particle size of the nimesulide particles is selected from the group consisting of less than 1900 nm, less than

1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1000 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

52. (Withdrawn) The method of claim 45, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

53. (Withdrawn) The method of claim 45, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

54. (Withdrawn) The method of claim 45, wherein the nimesulide or a salt thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined dry weight of the nimesulide or a salt thereof and at least one surface stabilizer, not including other excipients.

55. (Withdrawn) The method of claim 45, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the nimesulide or a salt thereof and at least one surface stabilizer, not including other excipients.

56. (Withdrawn) The method of claim 45, comprising at two surface stabilizers.

57. (Withdrawn) The method of claim 45, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, a non-ionic surface stabilizer, and an ionic surface stabilizer.

58. (Withdrawn) The method of claim 57, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides,

dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

59. (Withdrawn) The method of claim 57, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

60. (Withdrawn) The method of claim 57, wherein the surface stabilizer is selected from the group consisting of cationic lipids, polymethylmethacrylate trimethylammonium bromide, sulfonium compounds, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl

hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, polydiallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

61. (Withdrawn) The method of claim 45, utilizing as a surface stabilizer a random copolymer of vinyl acetate and vinyl pyrrolidone, hydroxypropylmethyl cellulose, or tyloxapol.

62. (Withdrawn) The method of any of claims 57, 59, or 60, wherein the composition is bioadhesive.

63. (Withdrawn) A method of treating a subject in need comprising administering to the subject an effective amount of a composition comprising:

- (a) particles of nimesulide or a salt thereof, wherein the nimesulide particles have an effective average particle size of less than 2000 nm; and
- (b) at least one surface stabilizer adsorbed on the surface of the nimesulide particles.

64. (Withdrawn) The method of claim 63, wherein the nimesulide or a salt thereof is selected from the group consisting of a crystalline phase, an amorphous phase, and a semi-crystalline phase.

65. (Withdrawn) The method of claim 63, wherein the effective average particle size of the nimesulide particles is selected from the group consisting of less than 1900 nm, less than 1800 nm, less than 1700 nm, less than 1600 nm, less than 1500 nm, less than 1400 nm, less than 1300 nm, less than 1200 nm, less than 1100 nm, less than 1000 nm, less than 900 nm, less than 800 nm, less than 700 nm, less than 600 nm, less than 500 nm, less than 400 nm, less than 300 nm, less than 250 nm, less than 200 nm, less than 100 nm, less than 75 nm, and less than 50 nm.

66. (Withdrawn) The method of claim 63, wherein the composition is formulated for administration selected from the group consisting of oral, pulmonary, rectal, ophthalmic, colonic, parenteral, intracisternal, intravaginal, intraperitoneal, local, buccal, nasal, and topical administration.

67. (Withdrawn) The method of claim 63, wherein the composition is a dosage form selected from the group consisting of liquid dispersions, oral suspensions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

68. (Withdrawn) The method of claim 63, wherein the composition further comprises one or more pharmaceutically acceptable excipients, carriers, or a combination thereof.

69. (Withdrawn) The method of claim 63, wherein the nimesulide or a salt thereof is present in an amount selected from the group consisting of from about 99.5% to about 0.001%, from about 95% to about 0.1%, and from about 90% to about 0.5%, by weight, based on the total combined dry weight of the nimesulide or a salt thereof and at least one surface stabilizer, not including other excipients.

70. (Withdrawn) The method of claim 63, wherein the at least one surface stabilizer is present in an amount selected from the group consisting of from about 0.5% to about 99.999% by weight, from about 5.0% to about 99.9% by weight, and from about 10% to about 99.5% by weight, based on the total combined dry weight of the nimesulide or a salt thereof and at least one surface stabilizer, not including other excipients.

71. (Withdrawn) The method of claim 63, comprising at two surface stabilizers.

72. (Withdrawn) The method of claim 63, wherein the surface stabilizer is selected from the group consisting of an anionic surface stabilizer, a cationic surface stabilizer, a zwitterionic surface stabilizer, a non-ionic surface stabilizer, and an ionic surface stabilizer.

73. (Withdrawn) The method of claim 72, wherein the at least one surface stabilizer is selected from the group consisting of cetyl pyridinium chloride, gelatin, casein, phosphatides, dextran, glycerol, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, dodecyl trimethyl ammonium bromide, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, hydroxypropyl celluloses, hypromellose, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hypromellose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and

formaldehyde, poloxamers; poloxamines, a charged phospholipid, dioctylsulfosuccinate, dialkylesters of sodium sulfosuccinic acid, sodium lauryl sulfate, alkyl aryl polyether sulfonates, mixtures of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), decanoyl-N-methylglucamide; n-decyl β -D-glucopyranoside; n-decyl β -D-maltopyranoside; n-dodecyl β -D-glucopyranoside; n-dodecyl β -D-maltoside; heptanoyl-N-methylglucamide; n-heptyl- β -D-glucopyranoside; n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β -D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl- β -D-glucopyranoside; octyl β -D-thioglucopyranoside; lysozyme, PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, and random copolymers of vinyl acetate and vinyl pyrrolidone.

74. (Withdrawn) The method of claim 72, wherein the at least one cationic surface stabilizer is selected from the group consisting of a polymer, a biopolymer, a polysaccharide, a cellulosic, an alginate, a nonpolymeric compound, and a phospholipid.

75. (Withdrawn) The method of claim 72, wherein the surface stabilizer is selected from the group consisting of benzalkonium chloride, polymethylmethacrylate trimethylammonium bromide, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, hexadecyltrimethyl ammonium bromide, cationic lipids, sulfonium compounds, phosphonium compounds, quarternary ammonium compounds, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride, coconut trimethyl ammonium bromide, coconut methyl dihydroxyethyl ammonium chloride, coconut methyl dihydroxyethyl ammonium bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride bromide, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride, C₁₂₋₁₅dimethyl hydroxyethyl ammonium chloride bromide, coconut dimethyl hydroxyethyl ammonium chloride, coconut dimethyl hydroxyethyl ammonium bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium bromide, lauryl dimethyl (ethenoxy)₄ ammonium chloride, lauryl dimethyl (ethenoxy)₄ ammonium bromide, N-alkyl (C₁₂₋₁₈)dimethylbenzyl ammonium chloride, N-alkyl (C₁₄₋₁₈)dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride,

trimethylammonium halide, alkyl-trimethylammonium salts, dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt, an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C₁₂₋₁₄) dimethyl 1-naphthylmethyl ammonium chloride, dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C₁₂ trimethyl ammonium bromides, C₁₅ trimethyl ammonium bromides, C₁₇ trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, polyquaternium 10, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearylalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, quaternized ammonium salt polymers, alkyl pyridinium salts; amines, amine salts, amine oxides, imide azolinium salts, protonated quaternary acrylamides, methylated quaternary polymers, and cationic guar.

76. (Withdrawn) The method of claim 63, utilizing as a surface stabilizer a random copolymer of vinyl acetate and vinyl pyrrolidone, hydroxypropylmethyl cellulose, or tyloxapol.

77. (Withdrawn) The method of any of claims 72, 74, or 75, wherein the composition is bioadhesive.

78. (Withdrawn) The method of claim 63, wherein administration of the nimesulide composition does not produce a difference in the absorption levels of the nimesulide composition when administered to a patient under fed as compared to fasting conditions, when administered to a human.

79. (Withdrawn) The method of claim 78, wherein the difference in absorption of the nimesulide composition of the invention, when administered in the fed versus the fasted state, is

selected from the group consisting of less than 100%, less than 90%, less than 80%, less than 70%, less than 60%, less than 50%, less than 40%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, less than 5%, and less than 3%.

80. (Withdrawn) The method of claim 63, wherein administration of the composition to a subject in a fasted state is bioequivalent to administration of the composition to a subject in a fed state, when administered to a human.

81. (Withdrawn) The method of claim 80, wherein “bioequivalency” is established by a 90% Confidence Interval of between 0.80 and 1.25 for both C_{max} and AUC, when administered to a human.

82. (Withdrawn) The method of claim 80, wherein “bioequivalency” is established by a 90% Confidence Interval of between 0.80 and 1.25 for AUC and a 90% Confidence Interval of between 0.70 to 1.43 for C_{max} , when administered to a human.

83. (Withdrawn) The method of claim 63, wherein the T_{max} of the nimesulide, when assayed in the plasma of a mammalian subject following administration, is less than the T_{max} for a conventional, non-nanoparticulate form of nimesulide, administered at the same dosage.

84. (Withdrawn) The method of claim 83, wherein the T_{max} is selected from the group consisting of not greater than 90%, not greater than 80%, not greater than 70%, not greater than 60%, not greater than 50%, not greater than 30%, not greater than 25%, not greater than 20%, not greater than 15%, and not greater than 10% of the T_{max} , exhibited by a non-nanoparticulate formulation of nimesulide, administered at the same dosage.

85. (Withdrawn) The method of claim 63, wherein the C_{max} of the nimesulide, when assayed in the plasma of a mammalian subject following administration, is greater than the C_{max} for a conventional, non-nanoparticulate form of nimesulide, administered at the same dosage.

86. (Withdrawn) The method of claim 85, wherein the C_{max} is selected from the group consisting of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, and at least 100% greater than the C_{max} exhibited by a non-nanoparticulate formulation of nimesulide, administered at the same dosage.

87. (Withdrawn) The method of claim 63, wherein the AUC of the nimesulide, when assayed in the plasma of a mammalian subject following administration, is greater than the AUC for a conventional, non-nanoparticulate form of nimesulide, administered at the same dosage.

88. (Withdrawn) The method of claim 87, wherein the AUC is selected from the group consisting of at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, and at least 100% greater than the AUC exhibited by a non-nanoparticulate formulation of nimesulide, administered at the same dosage.

89. (Withdrawn) The method of claim 63, additionally comprising administering one or more non-nimesulide active agents.

90. (Withdrawn) The method of claim 63, additionally comprising administering one or more non-nimesulide active agents effective for treating fever, inflammation or pain.

91. (Withdrawn) The method of claim 89, wherein said non-nimesulide active agent is selected from the group consisting of an analgesic, an anti-inflammatory, an antipyretic, and a vasomodulator.

92. (Withdrawn) The method of claim 89, wherein said non-nimesulide active agent is selected from the group consisting of nutraceuticals, proteins, peptides, nucleotides, amino acids, anti-obesity drugs, central nervous system stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, NSAIDs, non-nimesulide COX-2 inhibitors, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-

pharmaceuticals, sex hormones, anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, vasomodulators, and xanthines.

93. (Withdrawn) The method of claim 63, wherein the subject is a human.

94. (Withdrawn) The method of claim 63, wherein the method is used to treat a condition selected from the group consisting of rheumatic and joint diseases, arthritis, rheumatoid arthritis, osteoarthritis, periartthritis, tendonitis, bursitis, ankylosing spondylitis, joint stiffness, lower back pain, gynecological conditions, menstrual migraine attack, dysmenorrhoea, pelvic inflammatory disease, urological conditions, urethritis, prostatitis, and vesiculitis pyrexia, cardiovascular diseases, atherosclerosis, hypotension, thrombophlebitis, arthrosis; inflammatory conditions, otitis, rhinitis, sinusitis, pharyngitis, bronchitis nephrotoxicity, mastitis, asthma, cancer, trauma, surgery, migraine headaches, kidney disease, Alzheimer's disease, familial adenomatous polyposis, diarrhea, colonic adenomas bone resorption, and related conditions.

95. (Withdrawn) The method of claim 63, wherein the method is used to treat a condition where anti-inflammatory agents, anti-angiogenesis agents, antitumorigenic agents, immunosuppressive agents, NSAIDs, COX-2 inhibitors, analgesic agents, anti-thrombotic agents, narcotics, or antifebrile agents are typically used.